

Further news about the European Voluntary Harmonisation Procedure

The Voluntary Harmonisation Procedure (VHP) began in February 2009, but uptake so far has been slower than anticipated. The VHP still provides the fastest method for obtaining multiple trial authorisations within Europe. Report on [page 2](#) ▶

Revision of Detailed Guidance on CTAs and amendments

The EU Detailed Guidance on clinical trial authorisation (CTA) and substantial amendments is to be revised. A draft of the new document is now available for comment on the website <http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new_en.htm>.

Investigator's dual role leads to concerns

In investigator-led trials, one of the investigators often assumes the role of both investigator and sponsor. While this is permitted, it inevitably adds an extra dimension - and complications - to the study. Nevertheless, investigators who take on the additional role of sponsor must ensure that they comply with both sets of GCP responsibilities. See [page 4](#) ▶

More about ghost-written papers

The publication of ghost-written papers in medical journals is again causing concern. A major US pharmaceutical company has been accused of submitting articles that were not written by - or even the work of - their named authors. See [page 6](#) ▶

Woman dies during 'trial' of experimental drug

UK police have reopened their investigations into the death of a 22-year-old woman who collapsed and died after being injected with an experimental drug by her GP sister. More on [page 2](#) ▶

Investigator submits false data

Poor time management by a principal investigator may be responsible for the initiation of disqualification proceedings by the FDA. An inspection found that the investigator in Memphis, USA, had not performed physical examinations for at least six study subjects, despite signing the study records to indicate that he had done so. A Notice of Initiation of Disqualification Proceedings and Opportunity to Explain letter was issued by the agency. Details on [page 3](#) ▶

WHO/TDR adopts GCLP guidelines

The World Health Organization (WHO) and the Special Programme for Research and Training in Tropical Diseases (TDR) have released Good Clinical Laboratory Practice (GCLP) guidelines for trials in tropical countries. In April 2006, WHO and TDR met with other parties involved in clinical trials in disease-endemic countries to discuss the applicability of GCLP guidelines to their work. It was agreed that GCLP would be a valuable tool for improving and assuring quality laboratory practice in clinical trials in tropical settings. A working party of the Clinical Committee of the British Association of Research Quality Assurance had released a set of GCLP guidelines in 2003. TDR/WHO have since acquired the copyright to these guidelines and in March 2009 made them freely available for download from the Internet (see <<http://apps.who.int/tdr/svc/publications/tdr-research-publications/gclp-web>>).

Further news about the European Voluntary Harmonisation Procedure

The European Voluntary Harmonisation Procedure (VHP) began in February 2009, but uptake so far has been slower than anticipated. However, the VHP still provides the fastest method for obtaining multiple trial authorisations within Europe.

Sponsors of multinational trials seem to be hesitant to use the VHP. The procedure is a step towards a single multinational clinical trial authorisation (CTA). It is designed to make it both easier and faster to obtain national trial authorisations, compared with the existing approach of making individual CTA applications in full and then managing the separate sets of comments. There have been two successful applications via the VHP to date.

The VHP provides an ideal route for organisations developing medicines for pandemic diseases, who require fast authorisation to commence trials. The procedure has three phases:

- application to the VHP co-ordinator
- submission of the VHP dossier and review by participating national competent authorities (the VHP process)
- 'fast track' application to obtain national CTAs.

The process ensures that the national competent authorities of the countries to be included in the trial undertake a review within 30 days. If comments are

forthcoming from participating competent authorities, these are collated for the sponsor to address. Once VHP approval has been received, the sponsor should be able to obtain CTAs from each participating Member State within 10 days. Currently

- the VHP is open to any multicentre, multinational clinical trial using European investigator sites
- concerns about the requirement of the sponsor to respond within 10 days have been noted and there is some flexibility in this
- in the event that a Member State declines to participate in the VHP, the sponsor is free to deal with that Member State directly.

The scheme co-ordinators report that the method has worked well for those who have already participated. They encourage others to consider using this method for their next multinational trial with European centres.

Further information about the procedure may be obtained from www.bma.eu/uploads/media/VHP_public_CBB_22_Dec_08__bk_jan12.pdf.

Woman dies during 'trial' of experimental drug

UK police have reopened their investigations into the death of a 22-year-old woman who collapsed and died after being injected with an experimental drug by her GP sister.

Yolanda Cox experienced a severe allergic reaction after being injected with three times the normal dose of an experimental anti-ageing drug by her elder sister, Dr Yvonne Pambakian, in June 2007. It is now believed that the procedure was part of a test of the experimental product.

Ambulance staff were the first to raise concerns with the police. Dr Alexander Mackay of the Royal Free Hospital, London, commented that, "The

family were extremely reluctant to go into detail about the drug. I got the impression it was an experimental drug."

The drug was being developed by Amro Biotech, a biotechnology company set up by the sisters' mother. The company has spent over £3 million developing the drug over the last 10 years and both sisters worked for the organisation.

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Unknown element

During the inquest into Mrs Cox's death, Dr Pambakian stated that there was "always the element of the unknown" when giving a patient a drug as "you don't know how they will respond". She added that she had previously injected both herself and her mother with the drug, and that she did not know the exact dose because it had not been measured.

Dr Pambakian explained that the drug had been requested by Mrs Cox, who knew all about the product. The high dose had been given to achieve better results. She rejected the suggestion that they were all taking part in a drugs trial.

After her sister's death, Dr Pambakian was suspended from practising for more than a year by the General Medical Council. She has also been banned from prescribing drugs while an investigation into her conduct is completed.

The Medicines and Healthcare products Regulatory Agency has ordered the quarantining of all supplies of the product. A spokeswoman added that, "We are looking further into this matter and seeking legal advice."

Source: article by James Thompson, David Brown and Charlotte Chambers, The Times, 13 June 2009, p 10; <www.timesonline.co.uk/tol/news/uk/article6489149.ece>. This report by Sharon Jordan.

Investigator submits false data

Poor time management by a principal investigator may be responsible for the initiation of disqualification proceedings by the FDA.

Most trial sponsors expend a good deal of effort when selecting investigators and study sites with the qualifications, experience and expertise to conduct their trials. However, as trials become more complex, the time commitment from the on-site study team has increased.

While it is accepted that a principal investigator will delegate certain duties to other members of the study team, the sponsor must still be sure that the investigator has sufficient time to meet his/her study responsibilities. Principal investigators themselves must also be prepared to put aside the time needed to fulfil their obligations, and to ensure that those to whom they delegate tasks are legally permitted to undertake those tasks.

Deliberate falsification?

A recent Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter, sent by the US FDA to a Memphis investigator, demonstrates how having insufficient time to complete clinical trial responsibilities can have

far-reaching consequences.

Following an inspection, the FDA determined that the investigator had not performed physical examinations for at least six study subjects, despite signing the study records to indicate that he had done so. The study records for four subjects showed that the investigator performed their physical examinations on 6 November 2007, but the investigator's research appointment book noted that he was out of the office all week.

In response, the investigator wrote to the FDA stating that he had arrived at the research office at approximately 6.30 am on 6 November 2007 and performed assessments on "a couple of subjects", prior to leaving for the airport to attend a professional meeting. He further stated that, while he did not personally examine the other study subjects, his research staff performed the examinations and he later reviewed their findings and subsequently signed the date that the visit occurred. He said that he realised this is not standard practice, and that his staff should not have signed

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as completing the exam. He added that he should have dated his signature with the date on which he reviewed the exams. However, he failed to specify which subjects he examined and which were examined by his staff.

On the surface, it appears that this situation might have been avoided had the investigator considered his responsibilities more carefully. He could have made sufficient time to complete all the necessary physical examinations, rescheduled them to a more convenient time or properly delegated them to a suitably qualified study team member. Instead, based on this violation (and another where an ineligible subject had been enrolled into one study), the FDA determined that the investigator had

- failed to protect the rights, safety and welfare of subjects under his care
- repeatedly or deliberately submitted false information to the sponsor
- repeatedly or deliberately failed to comply with the cited regulations.

These actions were deemed to have placed unnecessary risks on the study subjects and to have jeopardised the integrity of the study data. As a result,

the FDA proposed that the investigator be disqualified.

This decision was communicated to the investigator in a NIDPOE letter, outlining the administrative proceeding being undertaken by the FDA to determine whether the investigator should be disqualified from receiving investigational products. The letter set out the options available to the investigator and the timeframe against which he must act. In particular, he was offered a consent agreement with the FDA regarding the future use of investigational products, and informed that entering into the proposed agreement would effectively terminate the disqualification proceeding. However, in the event that the investigator fails to respond to the NIDPOE letter or if the investigator's response to the FDA's allegations are considered unsatisfactory - or if an acceptable consent agreement cannot be reached - a regulatory hearing before the FDA will take place, where it will be determined whether the investigator should remain entitled to receive investigational products.

Source: <www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM143608.pdf>

Investigator's dual role leads to concerns

Investigators who take on the additional role of sponsor must ensure that they have a thorough understanding of both sets of GCP responsibilities.

In investigator-led trials, one of the investigators often assumes the role of both investigator and sponsor. While this is permitted, it inevitably adds an extra dimension to the study. A good deal of knowledge and organisation are required if the individual concerned is to meet both sets of GCP responsibilities. The situation is made more complex when the sponsor/investigator takes on multiple studies.

It is hoped that an individual who feels competent to take on both roles would have a thorough understanding of the regulations governing the conduct of clinical trials and would not make elementary mistakes. However, a recent

regulatory inspection revealed that a clinician acting as both investigator and sponsor in three trials made fundamental errors in both his roles.

Violation of investigator responsibilities

In his role as investigator, the clinician failed to meet requirements relating to informed consent:

- signed and dated informed consent documents were missing for two subjects
- the informed consent documents for two subjects were unsigned at some visits
- a subject had a magnetic resonance imaging (MRI) brain scan 2 days before giving consent

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- another subject underwent a liver biopsy on the day before providing informed consent
- several non-English speaking subjects were given informed consent documents written in English.

The clinician also neglected to ensure that an appropriate institutional review board (IRB) provided continuing review and approval of the studies. Several subjects continued to be enrolled, to receive study medication and to undergo study evaluations during periods when IRB approval of the relevant study had lapsed.

Finally, the inspector found a report sent to the Data Safety Monitoring Board (DSMB) and IRB that described an error in drug dispensing: placebo capsules had been included in a bottle that should only have contained investigational drug. As a result, the affected subject received only 50-90% of the investigational drug for 1 week of the study.

Violation of sponsor responsibilities

The sponsor is responsible for ensuring that all investigators are appropriately qualified to conduct the study and that the investigational sites have the necessary facilities, equipment and personnel. However, the inspection found that one investigator had participated in a study before a signed investigator statement had been obtained.

Furthermore, the FDA determined that the investigator/sponsor had not adequately monitored the studies. He stated that he was personally involved in the care and treatment of every subject at one site and had monitored their progress. He also stated that, in recent years, a DSMB had monitored the study data to assure patient safety. He accepted that he relied on other individuals at his institution to help ensure that the research was properly conducted at another site, and relied on a colleague at an academic institution to do the same at that site. He further admitted that he had failed to document monitoring activities adequately.

Finally, during the inspection the FDA was unable to find a curriculum vitae (CV) or

equivalent statement of qualifications for one investigator. The investigator/sponsor maintained that the CV was on file at the start of the study, but it could not be located during the inspection. As a result, the FDA concluded that the clinician had violated regulations that require a sponsor to retain specific study records and reports for 2 years after a marketing application is approved for a drug (or, if an application is not approved, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been notified of this final shipment).

Lessons to be learnt. Most of the investigator-related violations noted above are regularly reported as audit and inspection findings. However, those relating to the clinician's role as the study sponsor are more intriguing, in particular the use of the word "monitoring".

The FDA stated that the sponsor had not adequately monitored the studies. In his response, the clinician began by saying that he was personally involved in the care and treatment of every subject who participated in the studies at one site, and had monitored their progress. He also stated that a DSMB had been involved in monitoring study data.

In this part of his response, the clinician seems to be using the word "monitoring" to describe a different activity to that intended by the FDA. The clinician is referring to the monitoring of subject safety (ie. reviewing individual subject data and data across the study, to ensure that the welfare of individual subjects and the study population as a whole is being protected with respect to the effects of the study drug and procedures). However, while this is an essential part of clinical research, this is not the "monitoring" that the FDA means. In this context, the FDA is looking for evidence of the site monitoring usually undertaken by a dedicated clinical research

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associate or study monitor employed by the sponsor. Such site monitoring verifies that the study is being conducted properly, that case report forms and other study documents are being completed in a timely manner, that the protocol is being adhered to, that study medication is being stored and handled correctly, etc. The investigator/sponsor demonstrated his awareness of the need for site monitoring later in his written response,

by explaining that he relied on others to help assure that the research was properly conducted at each site, but that these activities had not been documented adequately.

The case does highlight the potential difficulties that a clinician might face in the area of study monitoring when taking on the dual role of investigator/sponsor.

Source: <www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm152450.htm>

More ghost-written papers submitted for publication

Although medical journals believe ghost-written articles to be dishonest and unacceptable, drug companies continue to submit them to enhance their chances of publication.

Ghost-written medical papers are again causing concern. A major US pharmaceutical company has recently been accused of submitting articles to medical journals that were not written by – or were even the work of – their named authors.

In January 2009 – following investigations by a US senator into the extent of the drug industry’s influence on healthcare – documents were disclosed confirming that ghost-writing is still occurring within the industry. It appears that the US drug company had come up with ideas for papers promoting its product, engaged medical writers and found respected experts to lend their names to the articles. The papers, on hormone replacement therapy, were then submitted to reputable medical journals for publication. The papers’ real authors remained anonymous.

More credibility

The term ghost-writing refers to the practice where articles are written by unacknowledged professional medical writers. When the articles are submitted for publication, a medical expert lends his/her name as lead author – sometimes for a fee – to add credibility to the content, despite not having been involved in the work described.

The World Association of Medical Editors (WAME)

has already issued guidelines that recommend strongly against ghost-writing. The involvement of professional medical writers is not in itself frowned upon; it is the fact that their involvement is not disclosed that worries WAME. Indeed, WAME states that, “Ghost authorship exists when someone has made substantial contributions to writing a manuscript and this role is not mentioned in the manuscript itself. WAME considers ghost authorship dishonest and unacceptable. Ghost authors generally work on behalf of companies, or agents acting for those companies, with a commercial interest in the topic, and this compounds the problem.” So papers that appear to be independent of drug company involvement are in fact not.

Another pharmaceutical company has also been accused of writing articles that cast a favourable light on its products. One editor, who unknowingly published such a paper, said she “considered that being scammed”. The drug company also produced its own journal, the *Australasian Journal of Bone & Joint Medicine*, which contained a collection of reprints of previous studies on the company’s products. Elsevier – who published the journal – subsequently said that it had been “hoodwinked”.

Source: article by Anjana Abuja, *The Times*, 23 May 2009, ‘The Review’ suppl, p 9. This report by Sharon Jordan.

News in brief

PhRMA clinical trial principles

The recently revised clinical trial principles of The Pharmaceutical Research and Manufacturers of America (PhRMA) aim to enhance the objectivity and transparency of clinical research.

PhRMA, which represents US pharmaceutical research and biotechnology companies, publishes a small number of principles and guidelines on its website. One of these relates to clinical trials.

PhRMA has formally endorsed measures to strengthen its Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results. The newly revised PhRMA Principles are part of an ongoing effort to help ensure the objectivity and enhance the transparency of clinical research. While the principles have no legal status, the organisation hopes that its members will adopt the revised standards when they take effect on 1 October 2009.

Among the changes, the revised PhRMA Principles will

- increase transparency, by committing companies to the timely registration of all interventional clinical trials involving patients (including some early Phase I studies) on a public website, thereby significantly increasing the amount of publicly available data on clinical trials
- adopt the authorship standards of the International Committee of Medical Journal Editors (ICMJE), so that only individuals who make substantial contributions to medical manuscripts will be recognised as authors
- enhance disclosure standards for published research sponsored by companies, by aligning with the ICMJE standards on the disclosure in medical journal manuscripts of all financial or personal relationships that might present a conflict of interest. In addition, authors of medical journal manuscripts will describe the role of sponsors in designing the study, collecting and interpreting data, and writing the report.

The revisions also bring the principles on company-sponsored clinical trial investigator meetings into line with the revised PhRMA Code on Interactions with Healthcare Professionals, which came into effect in January 2009.

Source: <www.phrma.org/news_room/press_releases/revised_clinical_trial_principles_reinforce_phrma%92s_commitment_to_transparency/files/PhRMA%20Marketing%20Code%202008.pdf>

FDA’s Transparency Task Force

The FDA has announced the formation of a task force to develop recommendations for enhancing the transparency of its operations and decision-making process. To support the

efforts of the task force, the FDA held a public meeting on 24 June 2009 to seek recommendations on how the agency can provide more useful and comprehensible information on its activities and decisions.

“Our administration is committed to making government open and transparent,” said Health and Human Services Secretary Kathleen Sebelius. “The Transparency Task Force will give the American people a seat at the table and make the FDA more open and accountable.” The task force will

- seek public input on issues related to transparency
- recommend ways in which the agency can better explain its operations, in a way that is compatible with the protection of confidential information
- identify information that the FDA should provide about specific agency operations and activities, including enforcement actions and product approvals
- identify problems and barriers to providing useful and understandable information about FDA activities and decision-making to the public
- identify appropriate tools and new technologies for informing the public
- recommend changes to the FDA’s current operations to improve the agency’s ability to provide information to the public in a timely and effective manner
- recommend legislative or regulatory changes, if appropriate, to improve the FDA’s ability to provide information to the public
- submit a written report to the commissioner on the task force’s findings and recommendations.

The establishment of the task force follows President Obama’s recent memorandum directing executive agencies to find new ways of making information available to the public, both rapidly and in a form that is easily accessible and user-friendly.

Source: <www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm163899.htm>

FDA review of older devices

The FDA has asked makers of certain medical devices to prove that their products are safe and effective. This step follows criticism of the FDA by the US Government Accountability Office in January 2009, for failing to fix its system for reviewing categories of devices that were allowed on to the market, prior to 1976, with minimal testing. The intention was that the FDA would reclassify them over time and determine where more extensive testing was needed. More than 30 years on, this review remains incomplete, and more than 200 high-risk medical devices have been approved via a process designed for low- and moderate-risk devices. The FDA has now asked several medical device companies to provide evidence of their products’ safety and effectiveness; the agency has given the companies 120 days to submit the required data. Regulators will review the data and classify the devices according to their risk.

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Exchange of inspection reports

A May 2009 revision of the document 'Guidance for Exchange of GCP Inspection Reports According To Article 15 (2) of Directive 2001/20/EC' has been issued. The Directive requires that an inspection report must be made available to the sponsor, while safeguarding confidential aspects. It may also be made available "to the other Member States, to the Ethics Committee and to the EMEA [European Medicines Agency], at their reasoned request". As inspection documentation is confidential and sensitive, the circulation of inspection reports is restricted and only allowed under certain circumstances. The updated guidance describes the process of the request, release and transmission of GCP inspection reports between the competent authorities of the EU Member States. The SOP has been revised to allow the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (which essentially brings together the individual authorising Member States in order to coordinate their activity) to be able to request the inspection report too.

Source: <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_05_13-exchange-gcp.pdf>

Exclusivity for biological products

Several bills have been laid before the US Congress in recent months relating to exclusivity rights for biological products. A further proposal in March 2009 has prompted responses from a number of key stakeholders, each of whom notes the importance of creating a regulatory framework that strikes a balance between the need for competition and strong incentives for investment.

The proposed bills will amend the Public Health Service Act to create a regulatory pathway for biosimilars. This would specify an exclusivity period, so that a generic company would have to wait for an extended period after the innovative biological product is first licensed, before the generic's own follow-on application could be approved. The individual bills can be differentiated according to the lengths of exclusivity period they propose, which range from 5 to 14 years; it is this factor that is seen as critical by industry representatives. The Pharmaceutical Research and Manufacturers of America appears to favour the possibility of a 14-year exclusivity period.

Source: <www.pbrma.org/news_room/press_releases/pbrma_statement_on_rep_esboo%92s_follow-on_biologics_bill/>

New look to Advisor newsletter

Advisor newsletter has had a facelift and modernisation!

This unofficial sample version of Issue 246 shows you how the newsletter will look, from Issue 247. We hope that you like it. Don't worry – the type of content will remain unaltered.

All newsletter information can be found on our website <www.canarybooks.com>

Principal Author & Editor: Prof David Hutchinson
Senior Contributors: Jane Baguley, Gareth Griffiths
Production Editor: Sharon Jordan

Senior Correspondents:

Joris Bannenberg, Gitte Raaschou Beck, Fabio Camarri, Pamela Charnley Nickols, Paul Chester, Sheelagh Corcoran, Hideki Fujiwara, Lisbeth Tofte Hemmingsen, Ezequiel Klimovsky, Julie Meeson, John Parker, Sam Tong, Colin Wilsher

Aim

To provide news and information to allow clinical research and quality assurance professionals, trainers, regulators, academics and members of ethics committees to stay up to date with clinical research and good practice developments.

Scope

Executive summaries of key laws and guidelines relating to clinical research in the ICH regions.

Summaries of relevant articles and information in other publications, press releases and information on the Internet.

Information on:

- changes in regulations, codes of practice, guidelines and new clinical research procedures
- news from important meetings and conferences
- ICH developments and progress
- news, views and opinions about ICH GCP implementation
- solutions to compliance-related problems
- inspection findings and lessons to be learnt
- clinical research methodology, statistical and legal issues
- quality assurance issues and procedures
- self- and independent audit practice
- training courses, jobs and other opportunities.

Sources of information

- We gather news from correspondents and other sources around the world.
- We gather intelligence from those actively involved in the regulatory process.
- We review the major medical, clinical research and QA journals.
- We search the web and regularly visit the websites of the major regulatory authorities in Europe, the USA and Japan, pharmaceutical industry and professional associations, major academic organisations and health associations.
- Sources of information, current at the time of publication, are usually quoted at the end of each article.

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Telephone: +44 1483 811383; Fax: +44 1483 812163

Email: info@canarybooks.com; website <www.canarybooks.com>

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